HEALTH EFFECTS

11) TITLE: Mechanisms of Cardiopulmonary Injury Caused by Mobile Source-Generated Fine and Ultrafine Particles

PROBLEM: There are strong associations between exposures to motor vehicle-derived particles and cardiopulmonary morbidity and mortality but there have been few studies that realistically examined possible differences in the effects of gasoline versus diesel-powered engine emissions. The Caldecott Tunnel, which has segregated traffic patterns, offers an opportunity to test the hypothesis that the health effects of diesel particles can be differentiated from those of gasoline particles with real world particles. Bore 1 is used by a mix of light-duty (LDV) and heavy-duty vehicles (HDV) while bore 2 is almost exclusively (99.8 percent) LDV (Gross, et al., Atmos. Sci. and Tech. 32: 152-163, 2000).

PREVIOUS WORK: Exposures to fine and ultrafine aerosols from diesel exhaust were shown to elicit allergic responses in chicken egg albumin-sensitized mice. This model was applied to determine whether exposures to freshly emitted particles from motor vehicle exhaust would also elicit airway allergies. A portable particle concentrator (VACES) concentrated fine and ultrafine particles drawn from air 50 and 150 meters from the edge of a heavily trafficked freeway system in Los Angeles and these particles were used to expose sensitized mice. Mice exposed 50 meters from the freeway exhibited elevations of cytokines and albumin-specific immunoglobulin, which are biomarkers associated with allergy-related changes in their airways. Mice exposed to purified air or concentrated particles 150 meters from the freeway did not have significant elevations of these biomarkers (Kleinman et al., JAWMA, in press, 2005). These particles were also shown to affect cardiac function and induce arrhythmias in rats.

OBJECTIVE: The objective is to test the hypothesis that there are mechanistic and outcome differences in the manner in which particles from LDV (mostly gasoline powered) elicit effects on health compared to HDV particles. Both vehicle types produce ultrafine particles that are capable of inducing pulmonary inflammation, however the HDVs emit about 50 times more particles than LDVs and the composition is not the same especially with respect to metals and reactive organic constituents. The toxicity of the fine and ultrafine particles in Bores 1 and 2 of the Caldecott Tunnel will be examined to test the hypothesis that inflammatory, cytotoxic and allergic responses will be elicited to a greater degree by HDV-derived particles, compared to LDV-derived particles, and that the acidity, reactive organic species content and metal content of the particles will influence the mechanisms of action and degree of toxicity in a dose-dependent fashion.

DESCRIPTION: Repeated inhalation studies will be conducted in the mixing plenum above Bores 1 and 2 of the Caldecott Tunnel. VACES will be used to provide adequate and matched concentrations of particles from the tunnel tubes. The concentrator will also effectively reduce the concentrations of gaseous co-pollutants (CO, NOX). Acute and chronic cardiopulmonary inflammation and injury will be examined using transgenic mice with specific knockouts or knockins along the NFkB and NRf2 signaling pathways to test specific mechanistic hypotheses regarding the roles of inflammation and oxidative stress in the development of pulmonary and cardiovascular injury. Endpoints will include measurements of cytokines and chemokines,

signal transduction mediators and histopathology. Samples to evaluate the physical and chemical composition of the particles will be collected during exposure and analyzed subsequently. In vitro tests will be performed to examine the potential of these particles to produce free radicals and to elicit cytotoxicity and heart muscle cell hypertrophy using well characterized cell systems.

BENEFITS: This study would provide critical information on the health effects from exposures to mobile source-derived PM using real-world aerosols. Knowledge of how differences between HDV and LDV-derived PM with respect to toxicity and corresponding health effects are critical to ARB's mission to protect public health.

12) TITLE: Physicochemical and Toxicological Assessment of the Semi-Volatile and Non- Volatile Fractions of Particulate Matter from Heavy- and Light-Duty Vehicles Operating with and without Emissions Control Technologies

PROBLEM: Recent emissions testing in either dynamometer or on-road testing facilities have shown that particles emitted from vehicles are externally mixed. Depending on vehicle type, age and ambient conditions, between 70-90 percent of the particles by number and 10-30 percent by mass may consist of more volatile material than others (known as semivolatile), and upon heating, will partially or completely evaporate (Sakurai et al., 2003). The exposure and health implications of these findings have not yet been investigated. Considering that the majority of people's exposure during their commute will be dominated (at least based on particle numbers) to these particles, it would be useful to know whether the non-volatile or semi-volatile material is more toxic.

PREVIOUS WORK: In addition to the aforementioned studies by the Southern California Particle Center and Supersite, (SCPCS), (Zhang et al., 2004) showed that that the volatility of traffic-generated particles explains the more rapid decay in their concentration with respect to distance from a roadway, compared to that of non-labile particulate matter species (such as elemental carbon) or gaseous co-pollutants such as CO and NOX. SCPCS studies (Kuhn et al., 2004) also showed significant shrinkage of these particles as they infiltrate indoors. Yet to-date, there is no information on the relative toxicity of these particles compared to the larger, non-volatile (refractory), mostly carbonaceous fraction.

OBJECTIVE: The objective is to determine the physicochemical and toxicological properties of the semi-volatile and non-volatile fractions of PM from heavy- and light-duty vehicles operating with and without emissions control technologies

DESCRIPTION: In this project, thermal denuders will be used, in conjunction with the University of Southern California particle concentrators (VACES), to investigate the relative toxicity of PM of different volatilities emitted from heavy duty and light duty, vehicles with/without PM filter traps and catalysts, using a dynamometer. The suspension of the collected PM will be used to determine whether particles of different volatility from different experimental configurations induce mitochondrial perturbation and reactive oxygen species (ROS) generation in a variety of different cell types such as macrophages, epithelial cells, endothelial cells, neuronal cells, renal cells and hepatocytes. The methodology for these toxicological evaluations is described in recent SCPCS papers by Li et al. (2003) and Xia et al. (2004) published in *Environmental Health Perspectives.*

BENEFITS: The semi-volatile PM fraction of vehicle emissions is extremely important in terms of its contribution to human exposure. Current emission control technologies remove effectively the non-volatile fraction, but not the volatile fraction. In fact, removal of the nonvolatile PM fraction has been shown to increase the concentration of the volatile fraction by enhancing nucleation of condensing organic vapors. Knowledge of how the toxicity of vehicular PM varies with particle component volatility will direct the design of emissions control technologies in order to better protect public health.

13) TITLE: Cardiovascular Health Effects of Ultrafine Particles During Freeway Travel

PROBLEM: Significant cardiovascular health effects are associated with exposure to fine particles. Specific causative agents are not known, but one likely suspect is ultrafine (<0.1 μm) particles. In urban areas the highest exposure to ultrafine particles occurs on freeways. Currently no clinical data on cardiovascular stress associated with pollutant exposure during freeway travel exists.

PREVIOUS WORK: Many epidemiologic studies have shown that short-term increases in ambient particles are associated with excess cardiovascular illness and death. Ultrafine particles, a component of PM2.5, show high toxicity in lab animals and enter the circulatory system when inhaled. Altered heart rate variability (HRV) is a known risk factor for cardiovascular morbidity, and has been observed in association with particle exposures. Ultrafine particles are found at high concentrations on and near freeways in Los Angeles.

OBJECTIVE: The objective is to determine if exposure to ambient air during travel on freeways changes HRV and other noninvasive measures of cardiovascular health and to determine if such changes increase with increasing levels of exposure to ultrafine particles.

DESCRIPTION: This is a clinical environmental study in which continuous measures of cardiovascular health and measures of fine and ultrafine particles would be performed, before, during and after a 2-hour exposure on a freeway. Twenty adult subjects will undergo continuous Holter electrocardiogram monitoring and periodic evaluation of cardiorespiratory symptoms and physiology (heart rate, blood pressure, arterial oxygen saturation), over a 26-hour period. Concentration and size distribution of fine and ultrafine particles, CO, and NOX will be monitored in the subjects' personal environment. In a control experiment at least two weeks later or earlier, the air breathed will be HEPA-filtered to reduce fine and ultrafine particle concentrations by at least 90 percent. Statistical analyses will test relationships between measures of exposure/dose and response within and between subjects. Second and third years will evaluate the dose response characteristics of these measures.

BENEFITS: This research will establish whether adverse cardiovascular health effects occur with exposure to freeway contaminants. It will demonstrate the efficacy of a convenient tool to assess the short term cardiovascular health impact of travel on freeways. This methodology can be used for future studies to evaluate the health impact of gasoline versus diesel dominated freeways, summer versus winter conditions, gas phase versus particulate phase contaminants. It has the potential to answer the question, which subfraction of fine particles is responsible for observed cardiovascular health effects.

14) TITLE: Particle Phase Peroxides: Concentrations, Sources, Behavior and Health Effects

PROBLEM: A class of biologically active species known collectively as reactive oxygen species (ROS) is a candidate for part of the adverse health effects caused by particle inhalation. In particles, the dominant ROS is hydrogen peroxide. In numerous *in vitro* studies, hydrogen peroxide at levels well below those expected for ambient samples has been shown to damage lung epithelial cells. Recently, an *in vivo* study showed that particulate hydrogen peroxide produced symptoms associated with respiratory distress, while gas-phase peroxides or ammonium sulfate particles alone did not, although particulate peroxide concentrations were not measured. A limited set of particulate peroxide concentrations have been measured in urban air, and show that peroxide levels are even higher than predicted by gas-particle partitioning.

PREVIOUS WORK: A technique to quantify peroxide levels in aerosols has been developed and has made limited measurements in urban air, finding that ROS levels are much higher than predicted by gas-particle partitioning. One other study in Taiwan found even higher levels, but were probably due to an analysis artifact.

OBJECTIVE: The objective is to measure aerosol-borne ROS concentrations at a variety of sites, investigating the relationship between these toxic compounds and location, source type, aerosol type, and photochemical activity. Additionally, laboratory studies on model systems and ambient samples will be carried out to determine the source and behavior of peroxides in aerosols, with particular attention to partitioning behavior on the time scales and humidities found in the lung environment.

DESCRIPTION: Size-segregated aerosols will be collected on filters and analyzed after extraction using high performance liquid chromatography/fluorescence. Aerosol water content will be measured with gas chromatography/thermal conductivity. Gas phase peroxides, particle mass, relative humidity, ozone, NO X, and other parameters will be monitored. Samples will be collected from representative sources including diesel and gasoline powered engines, in photochemically processed air, and at a forest background site. Aerosols will also be generated in a smog chamber. It is anticipated that many samples will be collected at sites co-located with on-going or planned studies (e.g., conducted by CARB, SCAQMD, USC-Children's Health Study and UCLA Supersite/Particle Instrumentation Unit) to take advantage of additional aerosol chemical composition and related data.

BENEFITS: Airborne particulate matter is strongly associated with the increased mortality associated with air pollution events. This study will investigate a highly oxidizing component of particulate matter, hydrogen peroxide, to determine its sources, prevalence, levels and behavior. Understanding the specific types of particulate matter toxicity is key to devising cost-effective control strategies that improve human health.

15) TITLE: **Investigation of the Relation of Traffic and Ultrafine Particles to Mortality in California**

PROBLEM: Although there are few studies relating adverse health effects to traffic-based pollution, several epidemiological studies suggest that residence near areas of high traffic density may be associated with respiratory symptoms in children, decrements in lung function, cancer, premature birth and mortality. Most studies, however, have relied on crude measures of traffic exposure; few have utilized measurements of localized pollutant concentrations, especially ultrafine particles (UFP or particles less than 0.1 micron). UFP are generated by both gasoline- and diesel-fueled vehicles and are of considerable research interest because of their demonstrated toxicological potential to induce oxidative stress and cause cellular damage. Given the dearth of studies on traffic-specific effects, it is important to undertake new studies examining their health impacts.

PREVIOUS WORK: A few time-series studies have reported associations between ambient PM2.5 and mortality. Several studies have linked UFP to inflammation, asthma exacerbation and other adverse health outcomes. A recent time-series study in Holland indicated that individuals who lived adjacent to a major highway had an increased risk of death associated with exposure to PM10 and Black Smoke. However, the pollution mix, activity patterns and exposures are likely to be quite different in California.

OBJECTIVE: The objective is to conduct an epidemiologic study of the relationship between daily mortality and alternative measures of traffic, including: (1) an exploratory analysis for the years 2001 and 2002 using the ARB's UFP monitoring at the Children's Health Study monitoring stations in southern California; and (2) an analysis of PM2.5-mortality relationships for the years 1999 through 2002 incorporating traffic metrics developed from geographical information system (GIS) software.

DESCRIPTION: This project will focus on the mortality impacts of residential proximity to traffic, based on both GIS-derived measures of traffic and some limited measurement of UFP. Spatial analysis, meteorological data, and census data to select the population (based on census tracts and block groups) likely to be represented by a given UFP monitor will be used. Investigators will then link these data with existing mortality data and emergency room data from local hospitals. Specifically, they will test whether a stronger association between PM2.5 and mortality exists for those living in census tracts, block groups or zip codes within a given distance (e.g., less than 150 meters from a major roadway). Such a study is now possible due to the existence of: (1) daily PM2.5 data for eight major counties in California for 1999 through 2002, and (2) concurrent mortality data with attributed addresses. Both sets of data have been made available for this project.

BENEFITS: This project would represent an important contribution to our understanding of the health impacts of traffic and UFP and will provide methodological insight to inform the design of future epidemiological studies. In addition, successful completion of this project may shed some light on issues of environmental justice, given that low-income and minority groups often live closer to major roadways than much of the population.

16) TITLE: Cardiovascular Disease and Asthma and Exposure to Long-term Air Pollution in the California Teachers Study Cohort

PROBLEM: Short-term ambient air pollution exposure has been implicated as a risk factor for exacerbation of pre-existing illness and for mortality in susceptible individuals. In contrast,

much less is known about: the health impacts of longer-term exposure, particularly on the development of cardiac or respiratory diseases and the roles of specific sources, especially traffic-associated emissions, with respect to the pathogenesis of chronic illness.

PREVIOUS WORK: California Department of Health Services (CDHS) staff members have collaborated with university researchers and the Northern California Cancer Center to establish the California Teachers' Study (CTS), a prospective study of 133,479 current and former female public school teachers and administrators recruited in 1995 from the California State Teachers Retirement System (mean age = 54 years in 1995). Follow-up data on disease incidence and mortality are currently available from 1995 through 2002. CDHS staff members have also developed several traffic exposure metrics using Geographic Information Systems that are considered state-of-the-art.

OBJECTIVE: To determine if long-term exposures to PM or to any of several gaseous pollutants are related to cardiovascular disease incidence or mortality and/or is exposure to traffic emissions, measured by residential proximity to busy roads, related to cardiovascular disease incidence or mortality. This project will also examine pollutant and traffic relationships with other health outcomes, including lung cancer and other respiratory diseases, as well as total mortality.

DESCRIPTION: Three series of detailed mailed questionnaires and computer linkages with California mortality and hospitalization databases will allow for examination of the incidence of mortality from diseases. Addresses of all participants have been geo-coded which will permit a more refined analysis of exposure to air pollution, especially to traffic exposures. Similarly, because prevalence of active smoking in this cohort is low (<5%) the database will allow for careful investigation of impacts of air pollution. This analysis would focus on the subset of study participants who live within 20 miles of fixed-site monitors. Multi-year averages of PM10, ozone, nitrogen dioxide, carbon monoxide, and several air toxics will be developed. The investigators will also utilize several years of PM2.5 monitoring and reconstruct additional fine particle data from airport visibility measurement. The primary analysis would also examine several traffic metrics, as well as long-term pollutant averages, as predictors of the health outcomes, using Cox proportionate hazards regression. Controls will include a variety of potential confounders and effect modifiers, including exposure to active and passive cigarette smoke, alcohol consumption, body mass index, and history of hypertension, dietary factors, and exercise.

BENEFITS: This effort would involve analysis of existing datasets and would leverage the infrastructure of a major ongoing study. The results would be the first to examine impacts of long-term traffic exposures on incidence and mortality from cardiovascular disease in the U.S., and would also be the first large cohort anywhere to examine the relationship of long-term air pollution exposure on the incidence of new cases of cardiovascular diseases.

17) TITLE: Traffic Pollution and Children's Health: Refining Estimates of Exposure for the East Bay Children's Respiratory Health Study

PROBLEM: Although epidemiological studies have documented associations between air pollutants and a variety of adverse health outcomes, the impact of exposure to traffic-based pollutants has not been well characterized. Most studies have used pollutant concentrations

measured at central monitoring sites and therefore could not examine the impact of residential proximity to major roads. In this light, the Office of Environmental Health Hazard Assessment (OEHHA) is proposing to develop new measures of exposure to traffic and to conduct additional analyses of a dataset developed specifically to examine the influence of traffic on children's respiratory health outcomes.

PREVIOUS WORK: OEHHA recently conducted a school-based, epidemiological study to examine respiratory health among children living and attending schools at varying distances from high-traffic roads in Alameda County, CA. OEHHA found that traffic pollutants measured at neighborhood schools were elevated near major roads and were associated with both bronchitis and episodes of asthma.

OBJECTIVE: The objective is to refine estimates of exposure to traffic-related pollutants in the OEHHA study through the integration of traffic, air pollution and time-activity data, using geographic information (GIS) methods.

DESCRIPTION: In a previous study, OEHHA related traffic-based air pollution monitored at schools to bronchitis and asthma episodes in children. School pollutant concentrations were used as surrogates for children's overall exposure to traffic emissions. The proponent will refine these measures to better reflect exposures at both residences and schools. By reducing exposure measurement error, they will obtain a better quantitative assessment of the health impacts of traffic on a vulnerable population. The study population is 85% non-white and generally of lower socioeconomic status, making this study a good opportunity to examine the effects of traffic on a low income and primarily non-white population. For this project, there is good coverage from CalTrans traffic data and only a few major highways, making it easier to model traffic exposures. Ultimately, these factors make it easier to isolate the effect of traffic on respiratory health, particularly among a sub-population where the issue of environmental justice is relevant.

BENEFITS: Results will be used to determine the relation of traffic exposure to health outcomes among a vulnerable population of children. It will evaluate the relative importance of different approaches to refining exposure estimates and will provide methodological guidance for future traffic studies. Finally, it will address issues of environmental justice for subpopulations who are often highly exposed to traffic, but whose pollutant exposures are not routinely monitored.

18) TITLE: Advanced Collaborative Emissions Study (ACES)

PROBLEM: Many of the most significant adverse health effects that are ascribed to exposures to diesel engine exhaust – including potentially increased risks for lung cancer – are premised on studies that relied on estimated exposures to diesel engine products from previous decades, specifically the 1960s and 1970s. The relevance of those studies and conclusions is becoming increasingly questionable, especially in light of the advanced diesel engines, aftertreatment systems, and ultra-low sulfur diesel (ULSD) fuels that will be entering the on-highway diesel vehicle market by 2007. Thus, there is a critical need for new emissions characterization and health studies of the exhaust from prototype 2007-2010 diesel engines equipped with advanced aftertreatment systems and operating on ULSD fuels.

PREVIOUS WORK: The Health Effects Institute (HEI) and the Coordinating Research Council (CRC) have been working in tandem to develop a detailed outline for the ACES program. HEI will be responsible for overseeing the health testing development, implementation and overall reporting of results. CRC will be responsible for overseeing the emissions characterization work of the ACES project.

OBJECTIVE: There are three principal objectives to the ACES initiative: (1) to produce a high-quality and health-relevant characterization of the emissions from advanced technology heavy-duty, on-highway diesel engines equipped with aftertreatment controls and operating on ULSD fuels; (2) to develop and apply best methods for researching and testing the potential public health implications of those emissions; and (3) to provide a state-of-the-science commentary evaluating the changes in emissions and potential risks from prototype 2007-2010 diesel engines.

DESCRIPTION: CRC will oversee a series of detailed studies to characterize and speciate prototype diesel engine exhaust, with special emphasis on ambient exhaust characteristics as may be experienced by a near-source receptor. HEI will oversee a series of health studies, including acute and chronic toxicity/inhalation studies, of the relevant prototype exhaust samples to assess both short and longer term potential effects of exposure, focusing on inflammation, asthma, allergic response, lung cancer and other key end-points. A synthesized commentary that can be used to inform public policy decisions pertaining to advanced technology diesel engines will be the final work product of the ACES program.

BENEFITS: The ACES program may provide useful, policy-relevant new information and background for an informed assessment of the technological advantages of advanced prototype diesel engines – greater fuel efficiency and reduced CO2 emissions to help address climate change concerns.